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CONTRACT NUMBER DAMD17-98-C-8023

TITLE: Demonstration of a Non-Invasive ICP Change Monitor

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REPORT DATE: September 1998

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 1998	Final (18 Dec 97 - 17 Aug 98)

4. TITLE AND SUBTITLE

Demonstration of a Non-Invasive ICP Change Monitor

5. FUNDING NUMBERS

DAMD17-98-C-8023

6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

The goal of the research is to design, build and demonstrate a device, which can be used on the battlefield, to diagnose blunt trauma injuries that can lead to increased intracranial pressure (ICP), and indicate the casualty's need for immediate treatment with drugs and evacuation to a facility equipped to handle brain trauma. The scope of the program described in this report involved fabrication and clinical testing of a device interfaced to laboratory data acquisition equipment with no realtime analysis software. Active Signal designed and fabricated the non-invasive ICP (NICP) monitor system and tested it on patients with ventriculostomies (pressure transduction of ICP from the lateral ventricles) or fiberoptic extradural pressure monitors in the Neurotrauma Critical Care Unit of the R. Adams Cowley Shock Trauma Center (STC) at the University of Maryland. Nine patients were monitored and comparisons between the NICP system and manometry data were made in combination with the patients status and outcome. This testing demonstrated the feasibility of using the NICP system to monitor pressure elevation and also the viability of the normal cerebral compensation mechanisms.

14. SUBJECT TERMS	15. NUMBER OF PAGES
intracranial pressure, ICP, change monitor, head injury, non-invasive, demonstration, clinical study	23
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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John McDowell 9-14-98

PI - Signature Date

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1. INTRODUCTION

1.1 Subject

Analyses of deaths resulting from injuries received in battle, especially from the Vietnam war, have shown that at least 80% of fatalities occurred within 60 minutes of receiving the injury[1,2]. While many of these perished before assistance could reach them, it has been estimated that a significant number (~30%) could have benefited from advanced biomedical intervention in the combat zone[1]. Among the types of wounds reported, head and chest wounds carried with them the highest probabilities of fatality (>80%) and so diagnostic tools and remedies for these wounds are critical to improving the survival chances of combat casualties.

Battlefield casualties with severe head injuries may develop internal swelling or other conditions that lead to increases in intracranial pressure (ICP), and, because this may occur rapidly with fatal results, it is imperative that the caregiver be able to monitor ICP and apply one of the known therapies to immediately treat any elevation. Unfortunately the changes in vital signs most classically associated with increased ICP frequently cannot be observed in a timely manner and so many physicians who care for head injury patients rely on some form of manometry to monitor ICP. A variety of sensors are available for this function but all involve drilling a hole in the skull. Such a procedure is clearly not suitable for battlefield emergency care whereas some of the therapies to treat elevated ICP can be applied in the combat zone and so the availability of a non-invasive, portable ICP change monitor will greatly enhance the treatment of a head wound casualty. This study explored the development of a device, which can monitor ICP changes non-invasively.

1.2 Purpose

The goal of the research is to design, build and demonstrate a device, which can be used on the battlefield, to diagnose blunt trauma injuries that can lead to increased ICP, and indicate the casualty's need for immediate treatment with drugs and evacuation to a facility equipped to handle brain trauma.

The overall technical objective of this program was to demonstrate a prototype of such an ICP change monitor and to describe the path to implementing it into a small system ready for battlefield training exercises. This overall objective was achieved by building on the work we had already done and answering some specific questions through meeting research objectives. These research objectives were divided into:

1. Duplicate experiments which indicate that the brain exhibits increased acoustic attenuation with elevation in ICP, and validate these measurements on a variety of patients at the R. Adams Cowley Shock Trauma Center (STC) of the University of Maryland at Baltimore. This objective was aimed at resolving the question of the range of applicability of the technique. While we did not expect to be able to extract absolute values of ICP from acoustic measurements using parameters from a generalized population of patients we needed to prove that a series of sequential acoustic measurements on a given patient can monitor ICP changes on that patient with a resolution to be determined from the clinical experiments. The extraction of absolute values of ICP from a given patient will require refinement of our model and curve-fitting of data by patient type -- which we did not sign up to do in this program. This more-difficult objective will need to be pursued in future work under separate funding.
2. Downselect from the variety of possible implementations of the brain interrogation methods to determine the optimum small system ICP change detection method. This objective was not

required to answer any fundamental questions regarding the technique but its achievement is essential to the practical implementation of a device.

3. Examine in detail the elements of a system which will allow such a device to be battlefield portable, capable of interfacing with other diagnostic systems and/or telemetry systems available for battlefield remote triaging. Again while not answering a fundamental question regarding the technique this analysis was designed to reveal whether there are any physical limitations, e.g., too much power required, too heavy etc., preventing the practical implementation of the device.

1.3 Scope of the Research

Active Signal has set out on the path to utilize its sophisticated sensor technology from the sonar world to demonstrate a small, non-invasive, portable ICP change measurement system capable of determining whether a head injury sustained on the battlefield is causing an increase in ICP. Using such a system, information relating to ICP change will be obtained real time, and will allow the medic or buddy to alert the next echelon care facility of the seriousness of the injury to assure immediate evacuation and life saving treatment. The scope of the program described herein involved fabrication and clinical testing of a device interfaced to laboratory data acquisition equipment with no real-time analysis software. Active Signal will deliver the sensors and mounting frame developed for the demonstration but not the data acquisition equipment. An optional task to complete and deliver a prototype system based on a laptop computer was not funded.

The scope of the research included the following items:

- Build a device which will be lightweight and readily attached to the skull for ICP trend monitoring
- Test the device at STC on a minimum of 5 patients
- Examine the data from the measurements as compared to the ICP measurements from the manometry equipment at STC
- Draw conclusions with respect to the implementation of the system in a self contained portable system suitable for combat casualty use

1.4 Background of the Previous Work

Traumatic Brain Injury (TBI) accounts for more than 75,000 deaths[3] per year in the United States -- more than half of all deaths from trauma -- and 99,000 disabilities[4]. The cost in years of productive life lost is estimated at more than $48.3 billion annually[5]. Death from TBI is the result of primary injury of brain tissue complicated by the secondary effects of ischemia, hypoxia, edema, and vascular spasm in the following days. Treatment of TBI focuses on the amelioration of secondary effects, but is complicated by our inability to directly monitor the perfusion of either injured or uninjured regions of the brain.

The cranium is an enclosed space, filled with three components: brain tissue, blood, and cerebrospinal fluid (CSF). Intracranial pressure, the pressure of the cerebral spinal fluid within the intracranial vault, represents a resistance to the perfusion of blood into the brain. The cerebral perfusion pressure (CPP) is equal to the mean arterial blood pressure (MAP) minus the ICP[6]. In normal young adults the MAP is in the range 85 - 90 mm Hg and ICP is 10 - 15 mm Hg so that CPP should normally be 70 - 80 mm Hg. Injury to the brain causes damage to cell membranes, with resultant edema of brain tissue and rise in ICP. Compensation is initially achieved by forcing CSF out of the cranium, but as swelling continues, the flow of blood into the cranium is impaired (lowered CPP) and perfusion of brain tissue suffers. Hypoperfusion leads to cellular ischemia,

then cellular injury and further edema. Secondary injury is thus perpetuated into previously uninjured portions of the brain until edema becomes sufficiently widespread either to reduce blood flow to zero or to herniate the brain stem, at which time the patient expires. Current clinical practice in TBI patients therefore relies heavily on the detection and correction of ICP.

Existing technology for monitoring ICP consists of one of several invasive devices, placed through a hole drilled in the cranium. Pressure can be measured from the dura by fiberoptic transduction or -- more invasively -- by threading a catheter through the brain to the lateral ventricle and directly transducing CSF pressure. ICP monitors must be placed by a neurosurgeon or highly trained assistant, and must be monitored by a specialized nursing staff in an intensive care environment. Risks associated with the procedure include the potential for laceration of a blood vessel, introduction of bacteria into the cranium, or direct injury to brain tissue. For these reasons, monitoring of ICP is limited to patients with severe TBI, and is continued for the shortest possible time. There is presently no clinical monitor available for patients with lesser degrees of injury, patients who have not yet reached an intensive care unit (e.g., battlefield casualties), or patients who have a contraindication to invasive monitoring. Development of such a non-invasive monitor will allow earlier and more aggressive monitoring of brain injured patients and facilitate earlier interventions to reduce or control ICP.

Three years ago, Dr. William Bernhard and Dr. Rick Dutton of the University of Maryland Medical System (UMMS) and engineering and scientific staff from Active Signal, who were working in antisubmarine Warfare sensor technology, explored the idea of a non-invasive low frequency (not ultrasound) acoustic method to determine ICP beginning with an investigation into the mechanisms of ICP change. Our discussions lead us to investigate resonance and impedance phenomena within the cranial structure as the ICP changes. We conducted preliminary tests using this approach and a teeter-totter to simulate ICP elevation. We pursued the same approach on cadavers under a small SBIR with Johns Hopkins, but were always lacking real data from individuals who were equipped with a subarachnoid bolt or intraventricular catheter. At this time we submitted our proposal for the work described here to the Medical Research and Materiel Command (MRMC) of the Army to develop and test a small system to monitor impedance changes in the brain as a function of ICP, and in the meantime continued development of the technique under internal funding.

The noninvasive intracranial pressure (NICP) assessment technique, developed by Active Signal, uses low frequency acoustic monitoring in a simple form that is markedly different from existing transcranial doppler ultrasonography (TCD). While both systems are non-invasive acoustic methods of assessing brain function, transcranial doppler uses high frequency ultrasound to determine blood flow in the larger arteries at the base of the brain[7], whereas NICP uses very low power audio frequency excitation to predict ICP elevations beyond 15 mmHg. It does this by exploiting low frequency attenuation phenomena excited by acoustic interaction with the fine structure of the cerebral vascular bed. These phenomena enable us to measure the active physiological response of the brain to externally applied stimuli such as routine endotracheal suction and chest percussion, and to track changes in mechanical consistency of brain matter. The brain blood flow assessed by Doppler is an important overall indicator of brain health, but does not necessarily correlate with ICP except in the very late stages of brain edema.[8] Although TCD and NICP both use acoustic interrogation, the system developed by Active Signal will be small, portable and inexpensive compared to the large TCD bedside device.

This is a pioneer field of inquiry and so the primary investigational method to-date has been extensive exploration and method refinement over a wide spectrum of experimental modalities, coupled with vigilant observation for trends that correlate with ICP or physiological state of the brain. Trends observed in healthy adults have been interpreted through the mathematical model we developed and compared with data measured on cadavers. The tools of measurement and analysis have been derived predominantly from the world of acoustic structural interrogation, and, antisubmarine warfare sonar, sensing and interpretation. These techniques span the range from

measuring transmitted amplitude levels, changes in signal attenuation, phase shifts, through to evaluation of noise characteristics, etc.

While the ultimate goal in all of these studies has been to establish an algorithm, or structure a decision tree, that can guide the disposition or treatment of a head-injured patient at the earliest stage of emergent care, our opening approach has been first to pull together all of the acoustical results and derived information in a completely open-minded "data gathering" -- due diligence type process. In our previous work the NICP technique had passed the following gates:

1) Demonstrated that the NICP measurement correlated with increases in ICP induced by head-down tilt on an inversion board on a number (>25) of healthy volunteers
   - clearly, absolute pressure could not be measured in this study for comparison with NICP
2) Produced a physically-meaningful mathematical model to describe the NICP measurements and give them a theoretical foundation
   - model results consistent with data on cadavers where acoustic levels were heavily depressed without cerebral perfusion

Now, with the data in this report, the initial data gathering task has been completed, enabling us to identify a few very promising indicators that will form the basis of a decision tree. In Section 2.3, Results and Discussion, it will be seen that certain factors stand alone as correlates of cerebral pressure elevation, some are reinforcing or confirmatory, and others reflect the viability of cerebral compensation and regulation mechanisms.

The Active Signal NICP system is distinct from other non-invasive methods of examining intracranial viability, specifically ICP. Other non-invasive systems include a host of patented but not commercialized methods and transcranial doppler. The latter is useful for late stages of brain edema but is effective only above 20 mm Hg.

Another ultrasound technique that seeks to measure ICP non-invasively is based on a time of arrival procedure[9] to track skull expansion with pressure which can work if the brain is a linear system and if there is predictability in skull structure, thickness uniformity, etc. In recent presentations by the inventors[10] it was clear that the system has not achieved it goals. In fact, Active Signal Technologies has also explored this technique at lower frequencies, and has found that the variables of individual differences, the variables in the acoustic impedance of the brain fluids, i.e. CSF, blood, and brain matter, which themselves vary as a function of the type of brain injury, render this approach unworkable.

Another assessment of this same effect came to the same conclusion.[11] We are aware of other non-invasive techniques involving ultrasound which operate on either blood flow patterns, velocity, arterial wall compliance or structural phenomena. The challenge with all of these systems is in the high attenuation as a function of distance, limiting transcranial penetration, unless high power levels are used. Conversely, low frequency acoustics provides less resolution, but its penetration depth is greater.

Although low frequency acoustic interrogation of the head has been discussed in the patent literature[12] for tracking shifts in the natural resonances of the bones of the skull with changing intracranial pressure, there are no reports of measuring and interpreting the much subtler interactions between an incident acoustic signal and the soft matter of the parenchyma, CSF and blood vessels. Interpolation of shifts in bone resonance is flawed since it assumes that the cranial vault can be considered filled with a fluid with the properties of water. Thus as the brain pressure increases, that structure's resonant frequency will also increase. The amplitude of the transmitted signal relative to the input signal will grow at the upper end of the band (above resonance) and

decrease at the lower end. Accordingly, an increase in signal level with increasing pressure is predicted above resonance, whereas we have found that signal levels decrease across the band studied. The reason for this decrease we believe is that compression of the vascular structure attenuates dynamic signals. For low frequencies, the transmission loss through the skull is minimal and the dominant effect is the acoustic property of the skull content not the skull itself, hence the attenuating property of that content as a function of pressure clearly dominates.

2. BODY OF REPORT

2.1 Experimental Methods

Active Signal designed and fabricated the non-invasive ICP (NICP) monitor system and tested it on patients with ventriculostomies (pressure transduction of ICP from the lateral ventricles) or fiberoptic extradural pressure monitors in the Neurotrauma Critical Care Unit of STC.

The details of the device used, a review of assumptions, procedures and measured data of the experimental design, are presented in the following subsections.

2.1.1 System Design

The NICP system, shown in Figure 1, measures the brain's response to sound over the frequency range 100 - 500 Hz. The acoustic signal is broadcast through a pair of transmitters contacting the head and is received by a contact sensor. The received signal and a reference from the signal generator are input to a spectrum analyzer. The type of signal currently used is a broad band signal comprising white noise in the band from 100-500 Hz, which enables 1 spectrum to be recorded in ~10 s. The data displayed is a frequency response which is calculated by subtracting the input signal to the amplifier from the receive signal at the sensor.

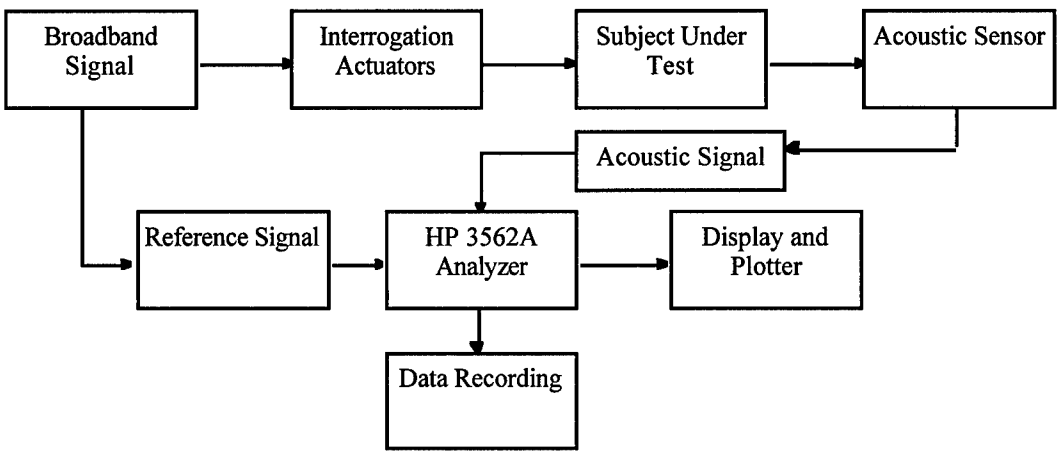

Figure 1. Block Diagram of NICP System

Figure 2 shows the NICP headband sensor unit mounted on a healthy volunteer. Interrogation of the brain is performed with a known source of acoustic input, and Figure 3 shows traces of the relative amplitude of transmitted sound, from Patient #1, spanning the measurement range of interest -- the higher acoustic signal corresponds to an ICP of 15 mm Hg and the lower to 50 mm Hg just after he had been suctioned. Analysis of the brain's acoustic properties over time produces direct correlations with changes in ICP as measured on invasive monitors, and more importantly, has the potential to provide information as to the source of those changes, whether from tissue edema or vascular phenomena.

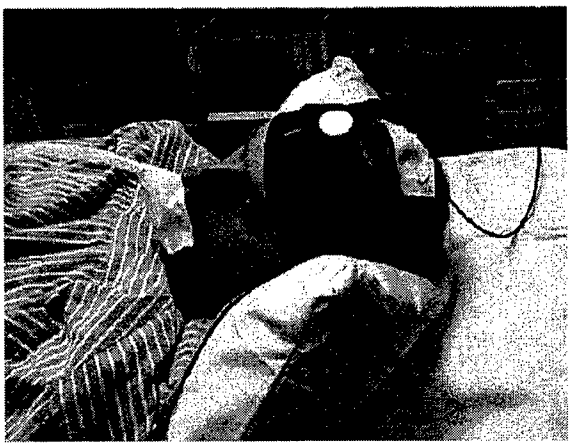

Figure 2. Transmitter and receiver components of the NICP system shown mounted on a volunteer.

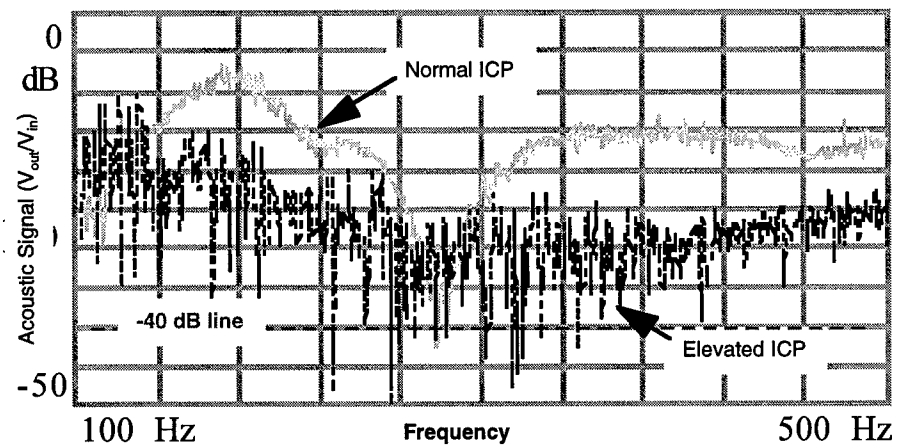

Figure 3. Broadband frequency response traces from Patient #1 showing signal reduction with elevated ICP.

As shown in Figure 1, a headband holds the transmitters and receiver in place with the transmitters positioned at the temporal area of the skull and the receiver positioned just above the sinus cavity on the forehead. The basis for the positioning is that both these areas are readily accessible without shaving the head, allowing the device in its proposed ultimate configuration to be used on persons at the scene of injury for early stage indicators of severity of brain injury. We discovered during the course of our testing that the location of the drivers is not critical to the fidelity of the data -- but that of the sensor is. The elements of the system are detailed below.

a) Transmitters/amplifiers: The transmitters or "drivers" are small hearing aid speakers, which are reconfigured to couple directly to the side of the head. Normally, there is one transmitter at each side. The frequency capability of the drivers is from 20 Hz to 15,000 Hz. A low voltage acoustic instrument amplifier is used and the pair of transmitters generates only low milliwatts of power.

b) Receiver: The receiver is a custom designed sensor which is so matched to the acoustic properties of the brain that it can discriminate changes in amplitude of sound transmission as fine as 0.1 dB, at frequencies from 50 to 2000 Hz. Because of this extreme sensitivity, the sensor has been custom-designed and refined to be very directional towards the head and have very low ambient noise response.

c) Acquisition System: The acquisition system includes a frequency analyzer (e.g., Hewlett Packard 3562 or 35665) and recording disc drives. The analyzer permits various

types of signal analysis, the most promising of which have been the frequency response measurements; time domain signal analysis; and power spectrum measurements. The measurements for the latter type of signals are those of very low frequency, i.e. brain pulsatile energy as emanating from cranial arteries.

2.1.2 Procedures

The NICP system was tested on patients, with informed consent, admitted to the Neurotrauma Critical Care Unit of the STC who have not had intracranial surgery, but have TBI severe enough to warrant continuous assessment of ICP by traditional means. Both patients with ventriculostomies (pressure transduction of ICP from the lateral ventricles) and fiberoptic extradural pressure monitors were eligible for study. One patient with an open skull wound and some patients who had undergone recent intracranial surgery were tested but will be excluded from future work because of the potential impact of these conditions on the acoustic properties of the brain and the difficulty of applying the NICP in the vicinity of surgical or traumatic wounds. We monitored 9 patients during the period of performance.

Informed consent was obtained from the patient's family, since the patients themselves are unable to communicate. Once this was done, the NICP monitor was applied to the patient's temples and forehead and data collection began. NICP output and invasive ICP and blood pressure were recorded approximately once every 10 minutes or when some patient activity occurred. The NICP technician noted on a time record any patient interventions likely to have an effect on the ICP: endotracheal suctioning, physical therapy, painful procedures, or moving in the bed are likely to elevate ICP; analgesic or sedative medications, diuretic therapy, elevation of the head of the bed, and drainage of CSF (when a ventriculostomy is present) are all likely to lower it. The NICP data recording equipment and technician were located remote from the bedside, so as to not interfere with patient care, but the technician could see procedures being performed and had a running record of the patient's ICP, MAP and CPP. Data collection continued for two to three hours, and was repeated the next day if the invasive ICP sensor was still in place. At the end of each data collection period we had parallel time histories of ICP, MAP and CPP together with spectral traces from the NICP and notes on events. Note that the NICP output is in the form of a series of "points" at regular time intervals where each point is a frequency response curve as shown in Figure 3.

One critical factor in selecting patients, conducting these tests and analyzing the data was our ability to group and categorize injury types, pathologies, and brain function viability. Based on CT and other conventional measurements and indicators, the patients will be grouped and their NICP data reviewed in light of this classification of symptoms.

2.2 Review of Assumptions

Our original hypothesis was that the brain is a closed fluid-filled structure that would cause the cranial structure's response to acoustic stimulation to change as ICP increased. The change could come in two forms, the first being a slight expansion of the cranial cavity that would cause a resonant frequency change and the second would be a variation in signal attenuation between driver and sensors located on the skull caused by a change in the consistency of the brain matter. We did not observe measurable resonant changes, perhaps because of internal damping, but we did observe consistent fluctuations in attenuation of the transmitted signal from the drivers to the sensors. This variation in attenuation would indicate that the energy that entered the brain at the temporal areas lost an increasing amount of energy with some variation in condition before the energy reached the sensor at the forehead. The reason for this attenuation we believe has to do with the increased impedance to flow within the fine vascular structure of the brain when it is

exposed to increased ICP. We then found that when ICP increased and CPP did also (within limits) that the resistance to flow did not occur, confirming our hypothesis. However, when either ICP was elevated and CPP remained the same or decreased, or when ICP remained constant and CPP fell, we noted that there was attenuation, leading us to conclude that the attenuation did have something to do with the mechanics of the brain obstructing dynamic flow in such a way that it attenuated dynamic signals with which we ensonified the brain.

2.3 Results and Discussion

During the course of the research we tested 9 patients, as described by Table 1, with the most salient results described below. Further definitive effort must build on these to form a decision logic tree applicable to patients from the earliest stages of injury on.

Table 1. Demographic summary of 9 patients monitored in 1998.

PATIENT			INJURY SCENARIO		ET*	HEAD INJURY PRESENTATION	GCS**		ACOUSTIC OBSERVATIONS	*Dispos-ition*
#	*Age*	*Sex*	*Date*	*Cause*	*(h)*		*A*	*D*		
1	24	M	3/15	Motor vehicle accident	38	facial fractures, basal skull fracture, subdural hematoma, tachycardic, no shock trauma, ICP normalized after 5 days	3	8	ICP range 6 - 30, very sensitive acoustic response	Rehab, Neuro impaired
2	21	M	3/29	Pedes-trian struck	44	epidural hematoma underlying depressed skull fracture, frontal subdural hematoma, cerebral edema, hemodynamically stable	6		ICP range 9-54, less sensitive acoustic response	TBI rehab center
3	19	M	4/27	Motor-cycle accident	65	seizures, basal ganglia hematoma, intra-ventricular hemorrhage, subarachnoid hemorrhage, diffuse shear, hydrocephalus	3	0	ICP range 18-57, virtually no acoustic response	Expired
4	45	M	5/4	Fall	68	bilateral frontal contusions with infarctions and subdural hematoma, minimal brain stem reflexes, sinus tachycardia	3	0	ICP range 21-32, low acoustic response	Expired
5	16	F	5/13	Motor vehicle accident	58	intraventricular hemorrhage, subdural hematoma, subarachnoid hemorrhage, temporal & basilar fracture	5	10	ICP range 3-29, acoustic response improved with time	Phys., occup., rehab
6	15	M	6/17	Motor vehicle accident	170	intracerebral hemorrhage, intraventricular hemorrhage, sinus tachcardia, hydro-cephalus, neuro sweats	3	6	ICP range 5-30, little change in acoustic response	Rehab
7	29	M	7/14	Motor vehicle accident	62	scalp laceration, intracerebal hemorrhage, C6 fracture, hemorrhagic falci at corpus callosum, diffuse axonal injuries	4		ICP range 8-27, acoustic response sensitive to ICP/CPP	Int. med. Care, stable
8	41	M	7/17	Fall	87	discharge records unavailable				
9	32	M	8/5	Gunshot	132	discharge records unavailable	3			

* E. T. = Hours of Elapsed Time After Injury Prior to Acoustic Monitoring

** GCS = Glasgow Coma Score (A=on admission, D=on discharge)

In accordance with an institutional review board (IRB) approved protocol incorporating informed family consent, as noted in the conditions of this contract acoustic trials were conducted at STC on Neurotrauma patients who had already been fitted with invasive cerebral pressure transducers. Although every attempt was made to obtain measurements on the patients as soon after admission as possible, by clinical necessity the trial had to be set up on a strict non-interfering basis, and it typically took 2-3 days before permission was obtained and monitoring could start without compromising the work of the attending medical staff. Each patient was monitored for several hours in more than one session where possible by observing the acoustical output at the forehead in response to preprogrammed low frequency audio input at the temples. To ensure that the data

was reproducible and meaningful, a careful study was made of all variables that could impact the measurement. For example, different methods were used to apply the acoustic signal to the head, such as broadband noise input with rapid averaging, swept frequency, and different ranges of frequency to ensure that the critical acoustic band was identified. Location of the transmitting and receiving transducers was varied, and alternative configurations were investigated, such as single sided sound projection versus bilateral transmitters.

Measurements were made and compared for reproducibility during quiescent periods and continued during periods were the ICP rose or fell either spontaneously or as a result of medical intervention such as patient movement, suctioning and the like. For the most part, these were transient events but in some cases the elevation or fall in ICP was sustained over long periods allowing us to examine steady state changes. During the course of each measurement, observations were made of all other pertinent medical data on the standard diagnostic instrumentation and monitoring display in each patient's room. The most important measures were obviously arterial blood pressure, ICP and CPP. In the following sections, we have summarized our observations in areas where reliable trends and correlations could be distilled from the data. It is these trends and correlations that are the underpinning for the algorithm / logic tree that will be used to extract medical indicators from the acoustic information.

2.3.1 Repeatability

Obviously, repeatability of acoustic readings is paramount to obtaining meaningful data, and real trends and indications must be sorted from experimental artifact, measurement scatter and physiological variability within normal ranges. At several points in the clinical trial, reproducibility was evaluated by collecting acoustic data at different times when all other variables were essentially unchanged. As shown in the example plot of Figure 2 for Patient #1, excellent reproducibility was obtained under constant medical conditions, giving us confidence that the effects we observed were associated with real changes in the acoustic response of the brain.

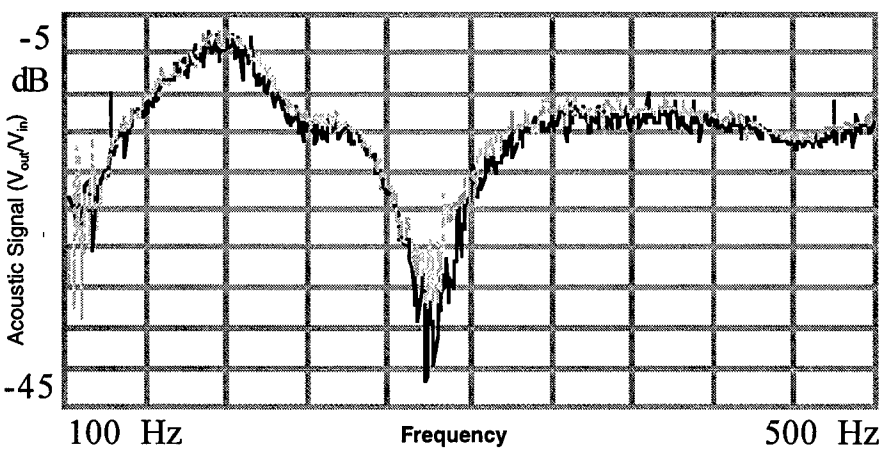

Figure 4. Example of repeatability of data -- Note high resonant level (marker) of ~6 dB.

This type of 1:1 overlay of the data was not only seen with all clinical cases but also in a long series of preparatory trials on healthy adult volunteers where ICP was temporarily elevated through body inversion to position the heart above the head. Cleanly reproducible traces were obtained in both the "normal" upright seated position and in the "high ICP" head down tilt -- repeatability even extending to measuring the same amplitude of apparent "noise" on the trace in particular frequency bands.

The severe dip in the center of the frequency response was commonly observed and was most often a function of sensor/driver location causing a destructive interference null in a particular frequency band. No correspondence was observed between the size or location of the null and patient status.

In contrast to the general pattern of repeatability, we have observed some variations in response. An example was collected at two different times, about an hour apart, on the same subject when his ICP and other physiological measures were essentially identical. The differences between the two measurements were later traced back to poor contact between the sensor and the skin during the later measurement because the sensor had become dislodged during patient movement. In all cases where there was no unusual movement of the sensor, the repeatability of measurements over the sample measured has been excellent. To avoid sensor movement after this discovery, a marking scheme was implemented on the patient's skin to highlight any movement, and medical adhesive tape was applied between the sensor and the skin.

2.3.2 Attenuation

In the clinical measurements to date, low frequency signal attenuation has been observed with increased ICP. Although this is a trend that is always in the same direction, the magnitude of the effect has not matched perfectly the size of the ICP change. One reason is described below under the heading of CPP and ICP correlations where we have discovered that attenuation is not a unique function of ICP and is at least as responsive to CPP as to ICP. Hence the acoustic attenuation corresponds to adverse changes in either or both CPP and ICP. Another factor, as discussed above, is that the majority of ICP increases are transient events lasting from a few 10's of seconds to a minute or two and our system was not being updated rapidly enough to track these.

Under some conditions, the attenuation accompanying ICP increase was quite subtle, in other circumstances, it was very pronounced. For example, when the injured person was monitored either soon after admission (less than 72 hours following injury) or while there was still significant unresolved edema (as in the case of Patient #1), attenuation with increasing ICP was quite noticeable as shown in Figure 5.

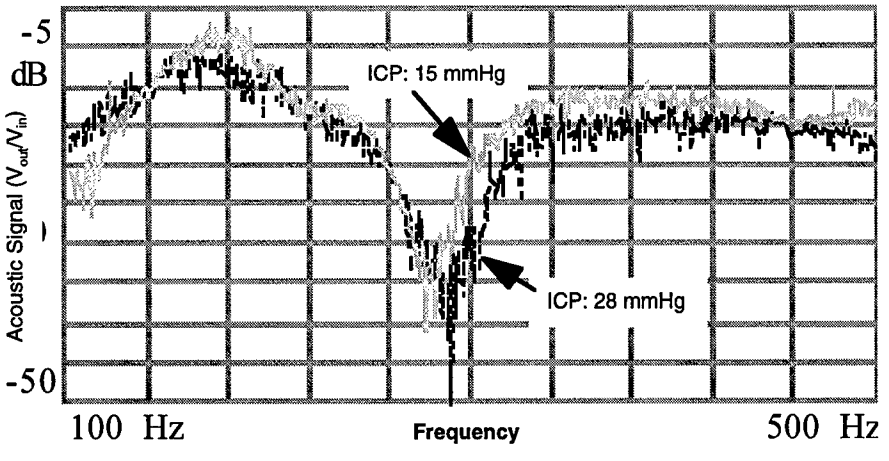

Figure 5. Trace change when ICP rose from 15 to 28 mm/Hg in Patient #1 – note general lower signal.

The lower trace in Figure 5 corresponds to the higher ICP level of 28 mmHg and is diminished in amplitude by approximately 4 dB across the band. In reviewing these results, it has to be born in mind that our waveform analyzer curves are very much raw, unprocessed data. As such, they show every fluctuation and detail of noise in the measurement, and do not discriminate salient from irrelevant features. For example, compared to Figure 3 the difference between the two spectral

responses in Figure 5 looks subtle as viewed on the logarithmic scale of the analyzer, however a 4-dB average attenuation translates to a very measurable 37% voltage drop. In the ultimate system, this very marked change could be captured simply and instantaneously as an RMS voltage reduction across the band, a difference in integrated area under the two curves, or an RMS voltage difference at a given frequency that is known to reflect a critical physiological indicator. By way of illustration, a parallel can be drawn between this and the development of the first pulse oximeter where examination of the raw IR spectrum showed little discernible relationship to blood oxygenation level. However, once the defining spectral line had been isolated, the tracking was perfect and it became quite simple to quantify and calibrate the system to read blood oxygen saturation directly.

An example of the diminished attenuation effect seen in some cases is given in Figure 6, where the ICP in Patient #2 fell from 54 mmHg to 10 mmHg over the course of quarter of an hour, but the higher ICP trace is only very slightly attenuated. In general, this patient exhibited very little acoustic response to ICP change. As opposed to the "systemic" increase in attenuation with pressure seen in other patients with sustained higher ICP levels, a different mechanism of ICP rise and fall is likely in this case. The medical staff attending this patient commented that the observed ICP increases and fluctuations were generally associated with blood pressure spikes resulting from vascular spasm accompanying external stimulation, whereas the baseline resting ICP was close to normal. Accordingly, the expected changes in acoustical properties of the brain as the vasculature clamps down with rising ICP might not be as evident because of the high perfusion pressure resulting from the increase in mean arterial pressure.

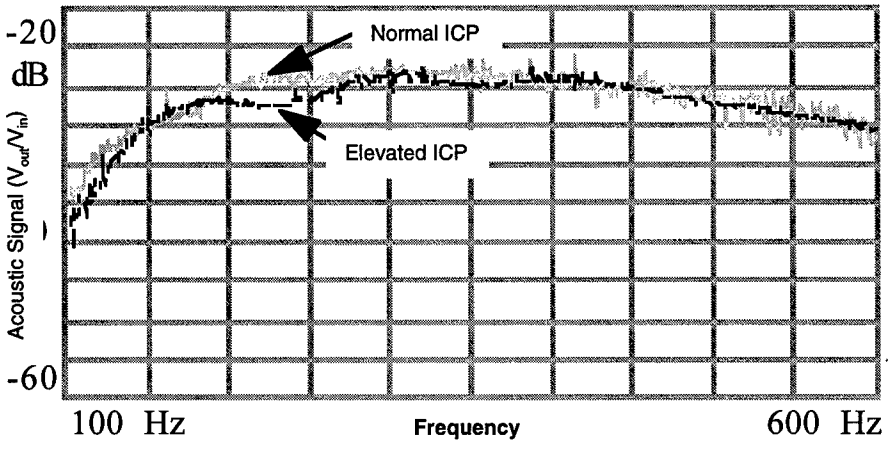

Figure 6. Significant change in ICP in Patient #2 produced only slight variation in signal level.

2.3.3 Absolute Signal Levels

In addition to the above described study of relative signal strength as ICP changes, we also examined the correlation in every case between patient condition and absolute signal level across the band. The results with two of the patients, who both had CT indications of severe brain injury, are particularly telling. Early measurements taken on Patient # 3 and Patient # 5 are shown in Figure 7 and exhibit almost identical acoustical spectral response – so similar, in fact, that the readings were checked and repeated several times after thoroughly checking the whole system for anomalous artifacts, improper signal analyzer settings, etc., to ensure that this was a reproducible measurement. What is remarkable, is not only the perfect overlay of the curves on two unrelated individuals (noting that even two different healthy adults produce very distinct and highly individual spectral response to acoustic excitation at the low frequency end), but the extremely low absolute level of the received signals. Whereas, the acoustic level from a normal brain, or an

injured but "viable" brain, is typically around > –30 dB through most of the frequency range of interest; at the time of this measurement, Patients # 3 and #5 were both responding at levels around –50 dB. Interestingly, low levels had also been measured in earlier work on cadavers conducted in association with the Neuro-critical Care group at the Johns Hopkins Medical Institutions. The inference is that when these measurements were taken, the cerebral vasculature was severely compromised in both of these patients. Patient # 5 had a hematoma at the time of the original test series, and Patient # 3 died a short time after testing. Days later, when the monitoring was resumed after the hematoma had resolved, the acoustic levels for Patient # 5 rose into the viable range of > –30 dB and she later recovered consciousness.

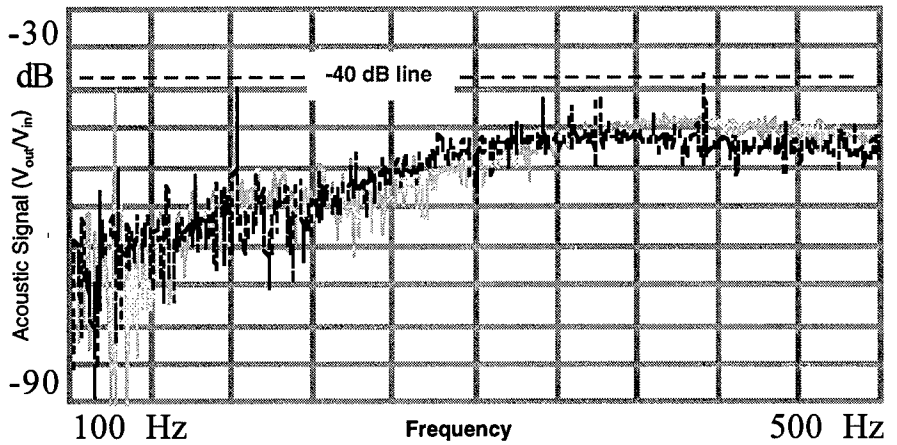

Figure 7. Similar and low levels of patients with serious and enduring brain damage at time of measurement.

2.3.4 Spectral Clutter

One of the more intriguing phenomena observed in the power spectrum received from the acoustically stimulated brain is the noise or clutter characteristics of the response curve. In the course of some of our earlier trials, we had seen a "ragged" response during ICP elevation, such as shown in Figure 6, particularly at the low frequency end of the band. Clearly this was a real physical effect because it appeared with either swept frequency excitation or broadband noise pulsing, it came through clearly after averaging over 10 sample traces, and was very repeatable from one scan to the next. Although we had initially dismissed it as random acoustic or electronic noise infiltrating the system at the low frequency end, it soon became apparent that there was a recognizable pattern to the appearance and disappearance of this "noise":

- It was never observed in our cadaver studies;
- In the clinical trials it normally appeared during patient stimulation in patients who recovered; and
- It was evident not only on brain injured subjects but also when the ICP was elevated in our healthy adult volunteers using either head-down tilt or transient bilateral jugular occlusion to stimulate a rise in ICP.

Again, the inference is that the ragged profile is an indicator of "healthy" or "normal" activity in the brain in response to ICP elevation. It might, for example, be a secondary effect caused by the brain's autoregulation and accommodation mechanisms counteracting the pressure increase.

The above phenomenon was commonly observed in the clinical trial during ICP transients. In particular, stimulation of a patient with TBI, as by suctioning the airway, causes a transient

elevation in blood pressure, which may lead to a rise in ICP in the edematous "tight" brain. The "noisy" transmission pattern in Figure 8, taken from Subject 2 is typical of this effect.

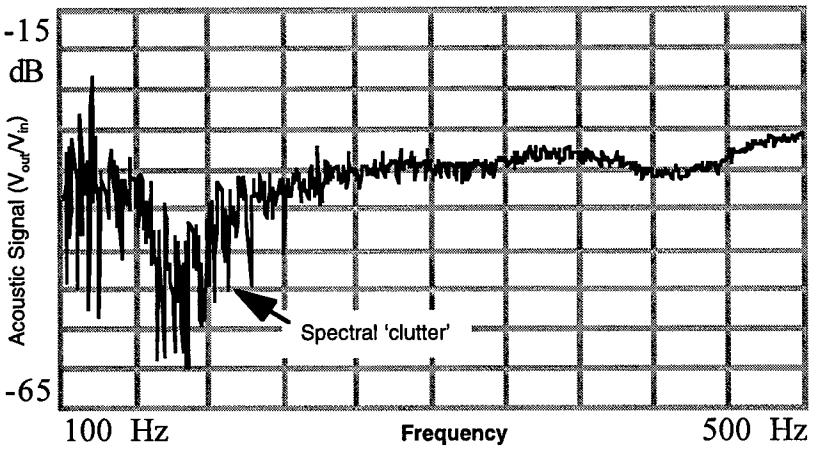

Figure 8. 'Noisy' trace character accompanying stimulation that appeared in most patients who recovered.

Another valuable piece of information comes from the observation that the noisy power spectrum can appear in response to pain or other stimulation even in the absence of measurable ICP increase on the invasive catheter. The example shown in Figure 8 is a case in point, where the invasively-measured ICP did not change significantly, the shape of the NICP transmission curve remained nearly constant, but the character of the trace became noticeably erratic during pain or excitation events.

Clearly, the noise phenomenon is tied to transient and non-steady state events and is not immediately interpretable as a quantitative measure. On the other hand, it has definite information content that can be used to confirm or reinforce inferences based on other measurements.

2.3.5 Relationship of Acoustic Response to Varying Levels of ICP and CPP

Although the primary focus of the program was to find non-invasively measured correlates to elevated ICP, clearly the underlying significance of high ICP, at least in the short term, is that it can compromise blood flow through the brain and hence cause life-threatening cerebral ischemia. CPP, the difference between Mean Arterial Blood Pressure (MAP) and ICP is generally maintained around 80 mmHg by vasoconstriction and dilation in the normal healthy brain, and thus represents both the driving force sustaining blood flow through the brain and provides a measure of the viability of its autoregulation mechanisms. Accordingly, CPP is just as critical a parameter as ICP in determining the medical status of a head-injured patient and assigning urgency of treatment. With this in mind, wherever the data was available to record MAP, ICP, CPP and preferably venous return, we also examined our acoustic data for correlation with CPP. Events of particular interest were ones where the ICP did not change but cerebral perfusion altered drastically in response to a drop in blood pressure. An example is provided in Figure 9, where CPP dropped from 79 to 54 in Patient #5 while there was essentially no change in ICP over the same period of time. The acoustic response showed precisely the same type of attenuation as observed with an increase in ICP. Again, while the visual separation between the curves is slight, the power difference between the two traces corresponds to a very measurable voltage drop of about 30%.

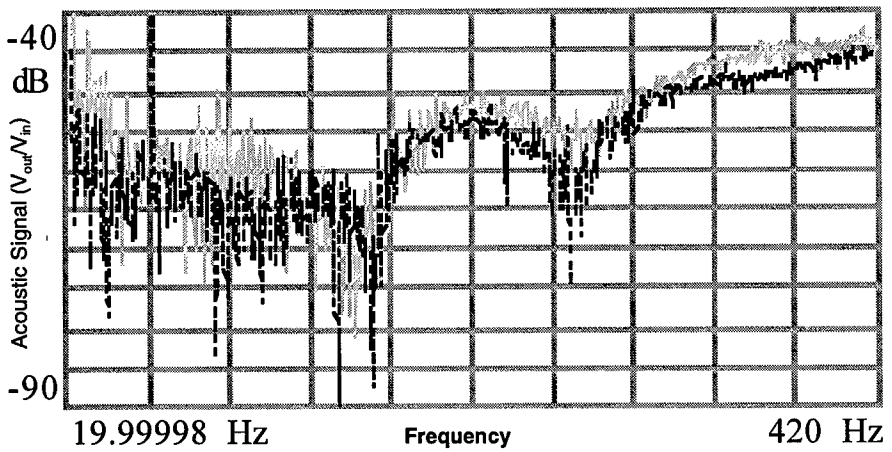

Figure 9. Signal traces for Patient #5 showing a distinct level variation over the band of measurement.

As shown in Figure 10 measured in Patient 5, both ICP and CPP remained constant (ICP 18, and 18, and CPP 63 and 62), and the levels are almost identical in the traces. While it may not be very clear in the trace comparison because of the tight overlay, note that one trace is noisier than the other. The noisier trace occurred soon after endotracheal suctioning. In another instance from Patient 5, when both ICP and CPP changed, with ICP higher and CPP lower, the trace showed attenuation, and the converse was true. Patient 6 displayed this same sensitivity to ICP/CPP variation. We have not yet captured data where ICP changed and CPP remained constant (the typical response of normal patients), nor do we expect to because we are only studying patients with severe TBI.

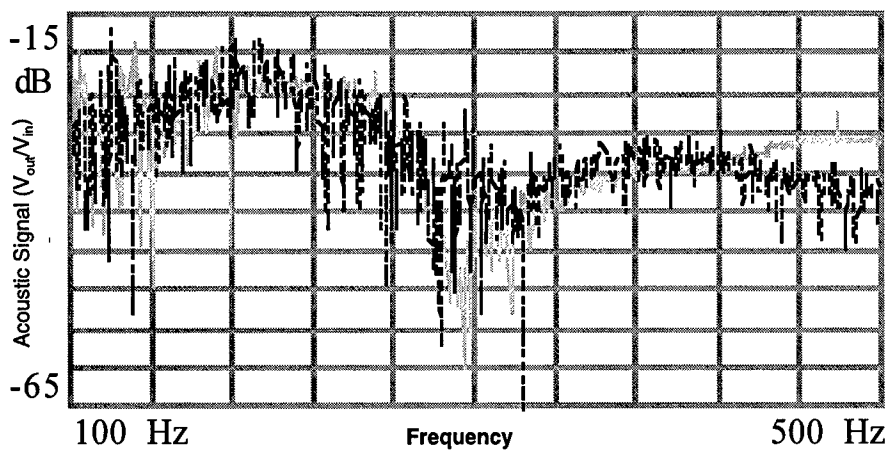

Figure 10. Traces from Patient #5 taken at identical levels of ICP and CPP.

The final approach we tested was to observe the shape of the waveform as detected passively through the forehead as a function of ICP change. An example of the shape and magnitude of this signal is shown in Figure 11 from Patient 6.

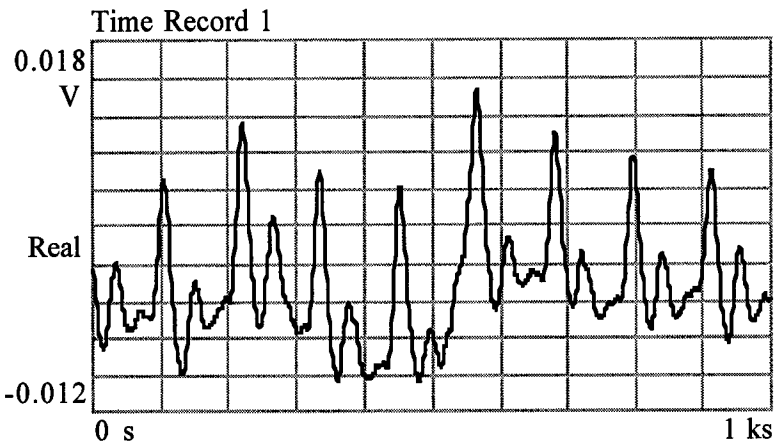

Figure 11. Arterial wave trace from Patient 6 in stable condition.

We continued to track this phenomenon in patients from #6 forward and found that indeed there was a correlation between ICP/CPP and arterial wave trace. In general, the amplitude decreased with increasing ICP and decreasing CPP. In one instance when the trend did not track, we found that it was traced to a vasoconstricting drug, dopamine, which skewed the results of the measurement, i.e. decreased relative amplitude.

Clearly, the implications of this last finding in the research are significant. This is the simplest form of measurement; i.e. arterial pulse in the closed vault of the brain involving a purely passive time based signal. Note that measurements conducted at the scene of injury (battlefield) will not be complicated by drugs because this assessment will occur prior to their administration. Finally, should we find that we can track amplitudes across patients from the normal to the seriously injured, we will have an established baseline when addressing the patient that will yield immediate information on patient condition. We will then proceed from this baseline to generate results which track ICP/CPP. While it remains to test this phenomenon on a body of patients, the initial results are extremely promising in the effort to develop an extremely lightweight, versatile, portable, ICP assessment monitor.

2.4 Problems in accomplishing the tasks.

With the assistance of STC staff, we encountered few problems in carrying out the research. We would like to have been able to monitor patients at the time of injury, but this was not feasible with a system that did not have FDA approval. Outside of that drawback, we were able to monitor patients from a sample population of male, female, over an age span of more than 30 years. We believe that our results are therefore representative and point to the valid conclusions from the study which we summarize in the next section.

Data analysis proved to be a very laborious task because of the shear volume of the data and the acquisition equipment not being automated. In order to examine trends we resorted to overlaying plots, as in the figures in this report, and manually comparing the plots to printouts of ICP, MAP and CPP. Clearly, if this important program is to proceed, the next phase must begin with development of a system with data acquisition on a computer so that statistical analyses can be performed on the data automatically.

3. CONCLUSIONS

The brief evaluation at STC has shown that significant differences could be observed across the pathologies tested -- differences that corresponded to severity and progress of damage to the brain, pressure elevation, and viability of the normal cerebral compensation mechanisms. We therefore believe that the NICP technique warrants more detailed clinical study to better demonstrate its tremendous potential and provide the basis for the algorithms to transform it into a standalone monitoring system.

The conclusions of this study are several and are positive:

1) Non-invasive intracranial pressure monitoring is not only feasible; it has now been demonstrated to be effective as a trend monitor.
2) The system works over the entire sample of the population we were able to test.
3) The measurements taken showed that the indicators were not only of ICP, but the more important clinical indicator of CPP or the ability of the autoregulation system to function when there has been brain injury.
4) The system also has the potential to be reduced in complexity if the final test indicators show that indeed we can monitor passively and get good information on trends.

With respect to the final item on our original tasks, it would be difficult to outline in detail how the system will be reduced in size for field use. This will ultimately depend upon whether the system has the complete capability of the transmit/receive measurement or whether only a passive measurement is required. In neither case will the system be complex—mostly a timed sensing mechanism with a peak or average detection system with associated logic to reduce the data or red/green indicators. Such a detection system has already been built for a vital signs monitor and we believe that a system with approximately the same level of complexity and sophistication would be most adequate for the final field ready ICP monitor.

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5. BIBLIOGRAPHY AND PERSONNEL

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5.2 Personnel Receiving Pay for this Effort

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Dr. Richard Dutton	UMMS	Principal Medical Consultant
Dr. William Bernhard	"	Associate Medical Consultant